REMARKS

Claims 1-72 were pending and subject to restriction. Claims 7, 9, 14-16, 34-42, 71 and 72 were withdrawn from consideration. Applicants reserve the right to file one or more continuing applications directed to the subject matter of these claims during the pendency of this application. Examined claims 1-6, 8, 10-13, 17-33 and 43-70 were variously rejected under 35 U.S.C. §§ 112, first and second paragraphs, 102, 103 and the judicially created doctrine of obviousness-type double patenting in a Final Office Action, mailed July 2, 2003 and reiterated in the Advisory Action, mailed October 20, 2003.

Independent claims 1 and 43 have been amended herein to make explicit what was previously implicit. In particular, it is now made explicit that the fusion molecules recited in the claims comprise a subunit protein of a chromatin remodeling complex (or functional fragment thereof), as described throughout the specification, for example on page 6, lines 1-13 and on page 24, lines 16-22. Further, these claims have also been amended to specify that contacting cellular chromatin with a fusion molecule comprising a DNA binding domain and subunit of a chromatin remodeling complex alters chromatin structure, as described throughout the specification as filed. Claims 8, 10, 12, 13 and 68 have been amended to properly depend from amended claim 1; and claim 5 has been amended to correct a typographical error. No new matter has been added as a result of these amendments and entry thereof is respectfully requested.

Obviousness-Type Double Patenting

Claims 1-6, 8, 10-13, 17-33 and 43-70 stand provisionally rejected under 35 U.S.C. § 101 as allegedly claiming the same invention as that of claims 1-15 and 17-20 of copending application no. 09/942,087. (Advisory Action, pages 3-4).

Applicants respectfully traverse this provisional rejection.

A determination of obviousness-type double patenting essentially involves the determination of obviousness under 35 U.S.C. 103, except that the patent principally underlying the double patenting rejection is not considered prior art. *See, In re Longi,* 225 USPQ 654, 684 (Fed. Cir. 1985). The examined claims are all directed to methods in which a subunit protein (or functional fragment thereof) of a multiprotein chromatin remodeling complex is used in a first fusion molecule to alter chromatin structure, not to regulate gene expression. In contrast, the cited claims of the 09/942,087 application are directed to methods in which a DNMT protein is used as a functional domain for repression of transcription. Although there are certain examined claims in which modulation of gene expression is facilitated by altering chromatin structure (*e.g.*,

claim 12), the chromatin-remodeling portion of the claimed fusion protein does not directly modulate gene expression, as do the fusion molecules described and claimed in 09/942,087. Rather, the action of the claimed fusion proteins (*i.e.*, alteration of chromatin structure), can facilitate the binding of a second molecule to cellular chromatin (*e.g.*, by exposing its target site), which second molecule then acts to modulate gene expression.

Furthermore, claim 43 explicitly recites that the first fusion molecule, comprising a chromatin remodeling protein (or functional fragment thereof) alters chromatin structure and that a second molecule modulates gene expression. As should be clear from the foregoing discussion, the attempt to equate "facilitating activation" with "regulation of gene expression" set forth in the Advisory Action, is incorrect. *See*, for example, page 6, lines 14-20; page 7, lines 10-13 and page 12, lines 5-11 of the specification for additional exemplary discussion of the distinction between modulation of gene expression, as claimed in co-pending 09/942,087 and alteration of chromatin structure (which may or may not facilitate modulation of gene expression), as claimed in the present application. For all of the aforementioned reasons, the pending claims are not obvious over co-pending claims 1-15 and 17-20 of 09/942,087; and withdrawal of the obviousness-type double patenting rejection is respectfully requested.

Rejections Under 35 U.S.C. § 112, Written Description

Claims 1-6, 8, 10-13, 17-33 and 43-70 were rejected as allegedly containing subject matter that was not described in the specification as filed. (Advisory Action, page 4).

For the reasons of record, Applicants again submit that the term "component of a chromatin remodeling complex," is defined in the specification as filed, and is understood in the art.[1] Indeed, references cited by the Office against the pending claims refer to a "component" of a chromatin-remodeling complex. *See, e.g.,* col. 21, line 47 of U.S. Patent No. 6,183,965 (Verdine).

Applicants traverse the statements concerning 35 U.S.C. 112, first paragraph on pp. 4-5 of the Advisory Action because the Office has taken certain phrases from the specification out of context, has failed to consider the teaching of the specification as a whole, has attempted to import limitations into the specification where none exist and has erroneously conflated the meanings of the words "can" and "may."

The Advisory Action asserts (pp. 4-5) that, because a particular passage from the specification uses the term "can comprise" to characterize the constituent proteins present in a chromatin remodeling complex, the passage "neither defines, nor limits what the 'component'

[1] See also the section of this response concerning 35 U.S.C. § 112, second paragraph

may be." First, Applicants wish to point out that the cited passage is not the only portion of the specification that describes a component of a chromatin remodeling complex. Indeed, Applicants have previously directed the Office's attention to numerous additional portions of the specification that further characterize, describe and provide exemplary support for the components of a chromatin remodeling complex. Second, because chromatin remodeling complexes comprise a large and diverse number of component proteins, it may not be possible for Applicants to enumerate each and every one of these proteins, nor may it be possible to provide a single underlying structural characteristic of a protein from a chromatin remodeling complex. Nonetheless, Applicants were the first to recognize that a fusion between a protein obtained from a chromatin remodeling complex and a DNA-binding domain could be used for targeted alteration of chromatin structure. Moreover, Applicants' specification has provided numerous examples of chromatin remodeling complexes and their constituent proteins. Thus, Applicants believe that they have defined a "component of a chromatin remodeling complex" as precisely and as thoroughly as the claimed subject matter allows. Applicants believe that any additional requirements for defining a component of a chromatin remodeling complex would prevent them from claiming what they believe to be their invention.

The Advisory Action also states: "Rather than defining the word component, this phrase [can comprise] merely suggests that the component **may** (emphasis added) be a constituent protein." Applicants respectfully assert that the foregoing statement takes the phrase "can comprise" out of context. The phrase is part of the following sentence: "A component of a chromatin remodeling complex can comprise one of its constituent proteins or a functional fragment thereof." Applicants' use of the word "can" in this sentence conveys the alternative possibilities that a component of a chromatin remodeling complex comprises either: (1) one of its constituent proteins, or (2) a functional fragment of one of its constituent proteins. Thus, taken in its proper context, the phrase clearly sets forth defining characteristics of a component of a chromatin remodeling complex.

Of far greater concern to Applicants is the assertion, in the Advisory Action, that the sentence "A component of a chromatin remodeling complex **can** comprise one of its constituent proteins or a functional fragment thereof" does not define the word component, but merely suggests what the component **may** be. The words "can" and "may" are different words and have different meanings, and the Office cannot re-define them at its whim. Webster's II New Collegiate Dictionary defines "can" to mean ability or possession, and "may" to refer to a certain measure of likelihood or possibility. Hodges Harbrace College Handbook states that "*[c]an* refers to ability and *may* refers to permission." Applicants chose to use the word "can" in that

portion of their specification, and it is entirely improper for the Examiner to rewrite Applicants' specification. Accordingly, the assertion that the use of the word "can," "merely suggests that the component **may** be a constituent protein," is traversed.

Finally, Applicants believe that, by focusing on the word "component," the Office is raising a red herring, by attempting to interpret (or re-interpret) a single word out of its proper context in the claims and supporting specification. The claims do not recite some undefined "component," they recite "a component of a chromatin remodeling complex." The term is defined in the specification to the extent that the subject matter allows and, as set forth above and in previous responses, numerous examples and descriptive material, relating to components of chromatin remodeling complexes, were provided in the application as filed. Accordingly, applicants respectfully request that the Office consider the claims as written, in their proper context, as supported by the totality of the specification, when assessing written description for claimed subject matter.

Notwithstanding the foregoing, the claims have been amended as shown above, solely to advance prosecution. Accordingly, withdrawal of the rejection is requested.

Rejections Under 35 U.S.C. § 112, Second Paragraph

Claims 1-6, 8, 10-13, 17-33 and 43-70 stand rejected as allegedly indefinite. (Final Office Action, paragraphs 19-20). In particular, it is asserted that the term "component of a chromatin remodeling complex" is not defined in the specification or claims, and that one of ordinary skill in the art would not know the metes and bounds of the claimed subject matter.

Applicants traverse, as they believe that one of skill in the art would readily understand that the term "component of a chromatin remodeling complex" refers to a polypeptide present in a multiprotein chromatin remodeling complex. *See*, for example, Cairns (1998) *Trends Biochem. Sci.* **23:**20-25, especially at page 21, first column, second full paragraph, wherein it is stated: "The yeast complex RSC (remodels the structure of chromatin) contains 15 **polypeptides**, and several **components** of RSC are strikingly similar to **components** of SWI-SNF."[2] (emphasis added) *See* also Knoepfler *et al.* (1999) *Cell* **99:**447-450, sentence bridging pages 448 and 449, wherein it is stated: "Both of these **proteins**, as well as the recently identified MBD3 **protein** . . . appear to be integral **components** of the Mi-2/NuRD complex . . ."[3] (emphasis added). *See* also Workman *et al.* (1998) *Ann. Rev. Biochem.* **67:**545-579, in particular page 569, first full paragraph, second sentence, wherein it is stated: "Deletion of genes that encode **components** of

[2] Reference AP-1 of IDS mailed on May 1, 2002
[3] Reference BJ-1 of IDS mailed on May 1, 2002

the SWI/SNF complex is not lethal to growth, whereas deletion of RSC **components** is lethal."[4] (emphasis added and noting that it is well known to those of skill in the art that genes encode proteins).

Moreover, the term "component of a chromatin remodeling complex," is defined in the specification as definitely and with as much clarity as the subject matter allows (see preceding section).

If the Office is aware of another plausible interpretation of the term "component of a chromatin remodeling complex"[5], consistent with the art of record (as discussed, in part, in this section), Applicants respectfully request that the Office set forth such interpretation, with supporting evidence.

Despite the clarity of this term as originally presented, claims 1 and 43 have been amended, solely to advance prosecution. Accordingly, the rejection can be withdrawn.

Rejections Under 35 U.S.C. § 102

Claims 1-5, 8, 10, 12, 13, 17, 18 and 68-70 were rejected under 102(e) as allegedly anticipated by U.S. Patent No. 6,183,965 (hereinafter "Verdine"). (Advisory Action, page 5).

For the reasons of record and those reiterated herein, Applicants traverse the rejection.

The pending claims recite a fusion molecule comprising a DNA binding domain and at least one subunit protein of a chromatin remodeling complex (or functional fragment thereof). In contrast, Verdine fails to disclose or suggest the claimed fusion molecules or methods for their use. Rather, Verdine discloses a system comprising two components. The first component is a "chimeric protein" comprising: (1) a DNA-binding domain and (2) a ligand-binding domain (*see* Verdine at column 26, line 10 through column 30, line 39). The second component of Verdine's system is described by Verdine as a "transcriptional modulator" and comprises: (1) a ligand which binds to the ligand-binding domain of the chimeric protein and (2) a "transcriptional modulating portion" or "TMP." Preferably, the TMP is a small molecule with a molecular weight less than 5 kD (*see* Verdine at column 3, line 65 through column 4, line 6; column 5, lines 16-29 and column 13, line 65 through column 14, line 8), not a protein. Figure 1C (reproduced below) of Verdine provides a schematic diagram of Verdine's system, in which the first component of Verdine's system (the "chimeric protein") comprises a DNA-binding domain labeled "GAL4" and a ligand-binding domain labeled "FKBP." The second component of

[4] Reference DB-1 of IDS mailed on May 1, 2002

[5] other than the curious notion that a hydrogen ion could be a component of a chromatin remodeling complex and would be capable of altering chromatin structure

Verdine's system is indicated in Figure 1C by a tubular structure (representing a ligand) attached to a twisted arrow (representing a TMP). *See* also legend to Figure 1B at column 4, lines 38-43:

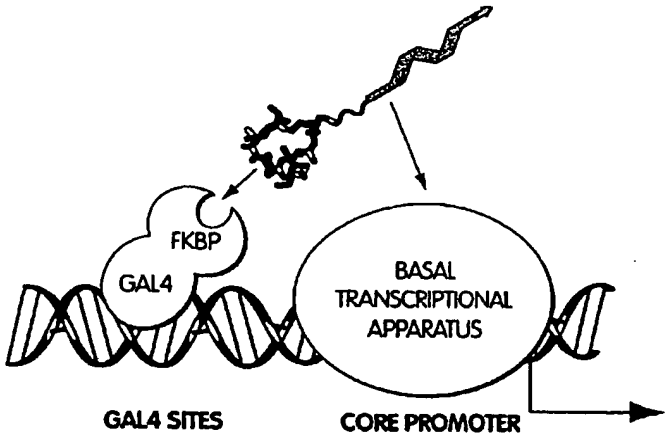
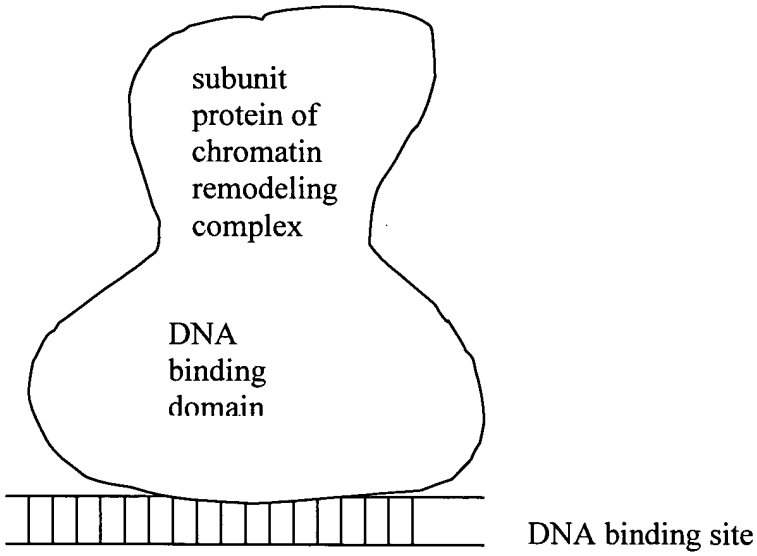


FIG. 1C

By contrast, the claimed fusion molecules can be schematically depicted as follows:



As can be seen by comparing the two systems, the only component of Verdine's system that could possibly anticipate is his first component, or "chimeric protein," since this is the only component of Verdine's system which comprises a DNA-binding domain. Whether or not the Office has made a *prima facie* case for anticipation thus depends on whether Verdine discloses

that the ligand-binding domain portion of his "chimeric protein" can be a component of a chromatin remodeling complex. In this respect, the Office has failed to point to explicit teaching, in Verdine, that his ligand-binding domain is a component of a chromatin remodeling complex; rather, the Office has resorted to selecting small passages from Verdine's disclosure, and combining them with each other, out of their proper context, to arrive at a reconstruction of the claimed methods.

For example, the Advisory Action states: "Verdine et al. teach at column 21, lines 27-28 'a transcriptional modulator that regulates gene expression by altering the chromatin structure'. *Thus, the transcriptional modulator is a part of a chromatin remodeling complex.*" (emphasis added). This statement takes the relevant passage from Verdine out of context; moreover, even assuming that the statement were not taken out of context, the Office's conclusion neither follows logically from the statement, nor is the conclusion supported by Verdine's disclosure. The complete sentence, from which the Office's quote was extracted, reads as follows:

> An example of a transcriptional modulator that regulates gene expression by altering the chromatin structure occurs when the transcriptional modulator, particularly its transcriptional modulating portion, **interacts** with chromatin-remodeling and/or modifying complex. (col. 21, lines 27-31 of Verdine, emphasis added)

It should be clear, from the full passage set forth above, that Verdine is teaching that his first component (chimeric protein) binds to DNA *via* its DNA-binding domain and to his second component *via* its ligand-binding domain. Verdine's second component (transcriptional modulator) binds to the DNA-bound chimeric protein *via* its ligand portion and, in this particular instance, might bind to a chromatin remodeling complex through its transcriptional modulating portion (TMP). This is very different from the claimed methods, in which a chromatin remodeling protein is itself part of a fusion molecule also comprising a DNA-binding domain. Accordingly, the passage cited in the Advisory Action, when taken in its proper context, fails to disclose or suggest the claimed methods.

Moreover, even when taken out of context, as it was in the Advisory Action, the cited passage fails to disclose or suggest the claimed methods. Verdine defines his "transcriptional modulator" as comprising two components (a ligand and a transcriptional modulating portion), neither of which is a DNA-binding domain. By contrast, the claimed methods recite a fusion molecule comprising a DNA-binding domain. For this reason alone, Verdine's statement that his

transcriptional modulator could regulate gene expression by altering chromatin structure fails to anticipate the claimed methods.

Furthermore, the Office's conclusion that "the transcriptional modulator is part of a chromatin remodeling complex" does not follow from Verdine's disclosure that his transcriptional modulator can regulate gene expression by altering chromatin structure; because Verdine's transcriptional modulators are disclosed as capable of regulating gene expression without themselves being part of a chromatin remodeling complex (see Verdine at column 21, lines 27-31, quoted above, in which the transcriptional modulator regulates gene expression by *interacting* with a chromatin remodeling complex).[6]

The Advisory Action extracts a second passage, also out of context, from Verdine's disclosure. The Advisory Action states: "Verdine et al. teach at column 22, lines 3-5 'the chimeric protein preferably includes at least one DNA-binding domain, a ligand binding domain and a transcription modulating domain'. Thus, the DNA-binding domain and the transcriptional modulator are comprised in a single fusion protein." The Office's conclusion appears to reflect a misunderstanding of Verdine's teaching,[7] as it appears to have mistakenly equated a transcriptional modulating domain with a transcriptional modulator, as defined by Verdine. A "transcriptional modulator," as defined by Verdine, comprises a ligand and a transcriptional modulating portion (TMP), preferably a small molecule (*see*, for example, column 3, lines 56-63; column 14, lines 30-39). By contrast, a "transcriptional modulating domain" as taught by Verdine, comprises a functional domain that activates or represses transcription, as described more fully in the paragraph following the one from which the Office's quote was extracted (Verdine at column 22, lines 6-20). Accordingly, Verdine does not in any way disclose a single fusion protein comprising a DNA-binding domain and his transcriptional modulator. Again, even assuming *arguendo* that he did, the disclosure of a chimeric protein including a DNA-binding domain and a transcriptional modulator (as defined by Verdine) would still fail to anticipate or suggest a fusion molecule comprising a DNA-binding domain and a subunit protein of a chromatin remodeling complex, as claimed; since Verdine fails to disclose that either the ligand portion or the transcriptional modulating portion (TMP) of his transcriptional modulator can be a subunit protein of a chromatin remodeling complex.

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[6] If the Office is attempting to redefine "chromatin remodeling complex" to include Verdine's transcriptional modulator, it is reminded, first, that the claims recite a fusion molecule comprising a DNA-binding domain and a subunit protein of a chromatin remodeling complex; second, that Applicants have provided clear identifying characteristics and examples of chromatin remodeling complexes in the specification; and, third, that the meaning of the term is well-known in the art. *See* also this response, in the sections concerning 35 U.S.C. §§ 112, first and second paragraphs.

[7] which is admittedly unclear in using the terms "transcriptional modulator" and "transcriptional modulating domain" to refer to different entities

To summarize, Verdine fails to disclose or suggest methods for altering the structure of cellular chromatin which involve the use of a fusion molecule comprising a DNA-binding domain and a subunit protein of a chromatin remodeling complex, or a functional fragment thereof. The art rejections are based on the isolation of small passages, out of context, from Verdine's disclosure and the misinterpretation of these passages, as discussed above. Nowhere does Verdine disclose or suggest a chimeric protein comprising a DNA-binding domain and a component of a chromatin remodeling complex, as claimed. Accordingly, the Office has failed to present a *prima facie* case of anticipation, and the rejection over Verdine should be withdrawn.

Rejections Under 35 U.S.C. § 103

Claims 1-5, 8, 10, 12, 13, 17-22, 27-30, 43-45, 47, 51-53, 56, 59 and 68-70 stand newly rejected under 103(a) as allegedly obvious over Verdine in view of U.S. Patent No. 5,972,608 (hereinafter "Peterson"). (Advisory Action, page 6). In addition, claims 1-6, 8, 10, 12, 13, 17-33 and 43-70 stand rejected as allegedly obvious over Verdine in view of Peterson and in further view of Cardoso and Omichinski. (Advisory Action, page 6). Finally, claims 1-6, 8, 10-13, 17-33 and 43-70 stand rejected as allegedly obvious over Verdine in view of Peterson and further in view of Cardoso and Omichinski and further in view of Rutter. (Advisory Action, page 8).

For the reasons of record and those set forth above, the primary reference (Verdine) does not teach or suggest the methods as claimed. Verdine's methods require that a chimeric DNA binding-ligand binding molecule interact with a separate chimeric ligand-transcriptional modulator portion molecule. Nowhere does this reference suggest that a fusion of a DNA binding protein and a subunit protein of chromatin remodeling complex could function on its own to alter chromatin structure (claims 1-33 and 68-70) or in combination with a second molecule to modulate gene expression (claims 43-67).

The secondary references do not supply what is missing from Verdine. Peterson is directed to assays and reagents for chromatin remodeling enzymes and is entirely silent as to DNA binding molecules. Further, claim 43 and claims depending therefrom do not, as suggested by the Office, require the use of two chromatin remodeling enzymes. (Final Office Action, first paragraph on page 15). Rather, these claims are directed to methods of modulating gene expression by contacting cellular chromatin with a first fusion molecule that alters chromatin structure and a second molecule that modulates gene expression. Neither Verdine nor Peterson teach or suggest such methods or such DNA binding domain-chromatin remodeling complex fusion molecules. Therefore, the rejection of claims 1-5, 8, 10, 12, 13, 17-22, 27-30, 43-45, 47,

51-53, 56, 59 and 68-70 as allegedly obvious over Verdine in view of Peterson should be withdrawn.

For their parts, Cardoso, Omichinski and Rutter contain no teachings or suggestions regarding methods of altering the structure of cellular chromatin as claimed. Indeed, Cardoso is concerned with analyzing the XNP gene product while Omichinski relates to elucidation of the structure and mode of binding a GAGA-factor DNA complex. Rutter relates to a single polymorphism in MMR and, as such, contains no suggestion to arrive at the methods as claimed.

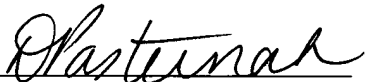
In sum, there is no combination of the cited references that would reasonably lead one of skill in the art to the claimed subject matter, must less any motivation to combine the cited references. Therefore, Applicants respectfully request that the rejections be withdrawn.

CONCLUSION

Applicants respectfully submit that the claims are in condition for allowance. If the Examiner notes any further matters which the Examiner believes may be expedited by a telephone interview, the Examiner is requested to contact the undersigned.

Respectfully submitted,

Date: December 2, 2003

By: 

Dahna S. Pasternak
Registration No. 41,411
Attorney for Applicant

ROBINS & PASTERNAK LLP
1731 Embarcadero Road, Suite 230
Palo Alto, CA 94303
Tel.: (650) 493-3400
Fax: (650) 493-3440